REMARKS

Reconsideration and withdrawal of the rejections of the claims, in view of the remarks herein, is respectfully requested. Claims 1-3, 8-11, 19, 21, 23, 25-37, 46, 48-54, and 58-69 are pending.

The 35 U.S.C. § 112, First Paragraph, Rejections

The Examiner rejected claims 58-59 under 35 U.S.C. § 112, first paragraph, as lacking adequate description or enablement, as the specification allegedly does not teach how to prevent splicing. The Examiner also rejected claims 25-26 and 68-69 under 35 U.S.C. § 112, first paragraph, as lacking enablement. Specifically, the Examiner asserts that as the claims are not limited to a specific therapeutic gene, promoter, enhancer or host cell, and there is no working example in the specification, in view of the low frequency of homologous recombination, a lack of published success for AAV concatamerization, and the unpredictability in the art, it would require undue experimentation to practice the invention without employing a selectable marker. These rejections are respectfully traversed.

First, it is within the skill of the art to analyze transcripts from a particular transcription unit via molecular biological techniques, e.g., RNA extraction and gel electrophoresis, to determine whether a transcript is spliced (see the abstracts for Christiansen et al., Hum. Mutat., 14:222 (1999), and Lemire et al., Arterioscl. Thromb. Vasc. Biol., 19:1630 (1999), enclosed herewith). It is also within the skill of the art to scan a sequence, e.g., with software, to identify potential consensus splice donor and splice acceptor sites. Therefore, it would not require undue experimentation to prepare vectors that lack splice sites.

With regard to AAV concatamers, there were reports of AAV concatamer formation prior to Applicant's effective filing date (see the abstract for Vincent-Lacaze et al., J. Virol., 73:1949 (1999), Bertran et al., Ann. N.Y. Acad. Sci., 850:163 (1998), and Duan et al., Virology, 211:8 (1999), a copy of each is enclosed herewith, and see Example 2 in the specification). Moreover, Applicant's specification provides evidence of heteroconcatamerization of AAV genomes (see Examples 5-7).

With regard to Capecchi (Science, 244:1288 (1989)), a document cited by the Examiner to support the proposition that recombination frequencies are low, the Examiner is requested to

consider that Capecchi relates to homologous recombination in genomic DNA (e.g., 1 copy of the target per haploid genome). In contrast, Applicant's invention relates to viral vectors, i.e., AAV vectors, where numerous targets, e.g., hundreds to hundreds of thousands of AAV DNA targets, for recombination may be present in a cell. Given the numerous targets for recombination, and the sensitive measures available to the art to detect expression, a selectable marker is not required to practice the invention.

The Examiner is also reminded that broad claims and the absence of a working example are not sufficient to conclude that the specification is nonenabling. In particular, there is no requirement for a working example to fulfill the requirements of 35 U.S.C. § 112, first paragraph, if the invention is otherwise disclosed so that one of ordinary skill in the art can practice the invention without undue experimentation. In re Robins, 166 U.S.P.Q. 552 (C.C.P.A. 1970); In re Borokowski et al., 422 F.2d 904, 164 U.S.P.Q. 642 (C.C.P.A. 1970).

Applicant discloses the use of AAV vectors for "*cis*-activation" (see, for instance, page 10, lines 9-20 and Figures 20-21), i.e., a regulatory element(s) in one rAAV vector that is introduced into cells can regulate in *cis* expression of a transgene delivered by another rAAV, which is in contrast to "*trans*-splicing," i.e., the use of splicing vectors (page 91, lines 9-18 and Figures 19 and 25). For instance, at page 6, line 26-page 7, line 8 of the specification, it is disclosed that, with respect to gene therapy with rAAV, large regulatory elements and genes beyond the packaging capacity of rAAV can be brought together by co-infecting with two independent rAAV vectors. It is disclosed that in one embodiment, one vector has an enhancer and/or a promoter and the other vector has an open reading frame of interest with or without a minimal promoter ("*cis*-activation"). After coinfection with the two vectors, it is disclosed that transgene size in increased beyond that for a single AAV vector and the open reading frame is linked to the enhancer and/or promoter (page 7, lines 3-6). At page 91, it is disclosed that through concatamerization, two vectors for *cis*-activation are brought together allowing for *cis*-activation of enhancer/promoter combinations (Figure 21).

Moreover, the Examiner cannot rely on a citation in the M.P.E.P. without more to conclude that "the art in general is acknowledged to be unpredictable" (page 6 of the Office Action). Applicant respectfully traverses this assertion as a form of Official Notice for making a conclusory statement without support of a reference. Applicant respectfully requests a reference

to support the assertion or an affidavit of personal knowledge by the Examiner in the next official communication.

It is Applicant's position that in view of the specification, Applicant has enabled and described the claimed invention. Therefore, withdrawal of the 35 U.S.C. § 112(1) rejections is respectfully requested.

The 35 U.S.C. § 103 Rejection

The Examiner rejected claims 60-62 and 65 under 35 U.S.C. § 103(a) as being unpatentable over Doll et al. (Gene Therapy, 3:437 (1996)). This rejection is respectfully traversed.

Doll et al. compared promoter strengths in mammalian brain cells using AAV vectors. Four different promoters or promoter/enhancer combinations were linked to a LacZ open reading frame flanked by AAV ITRs (see Figure 1) and those constructs were used to prepare recombinant AAVs (rAAVs). Each rAAV was individually introduced to mammalian brain cells and LacZ expression detected.

Doll et al. do not disclose or suggest introducing two AAV vectors to a cell, a point acknowledged by the Examiner on page 3 of the Office Action, much less introducing two AAV vectors to a cell where a promoter in one AAV vector regulates the expression of an open reading frame in a second AAV vector.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to adapt the vectors used by Doll et al. to separate the promoter/enhancer from the therapeutic gene and utilize a two vector system to introduce DNA into cells because it provides the benefits of additional packaging space and providing for interchangeable vectors. Clearly, the Examiner is using impermissible hindsight, i.e., the benefit of Applicant's disclosure, to arrive at this assertion (see page 7 of the specification).

Moreover, the Examiner has failed to consider that the ITR formed between two AAV genomes in a concatamer contains promoter elements. Thus, one skilled in the art, prior to Applicant's disclosure, would not expect that a heterologous promoter in one AAV vector could regulate transcription of a gene product in a different AAV vector because of possible interference by the ITR formed between two AAV genomes in a concatamer.

Further, the Examiner cannot logically have it both ways, asserting that the invention is unpredictable (see the 35 U.S.C. § 112(1) rejection above) yet obvious.

Accordingly, withdrawal of the 35 U.S.C. § 103(a) rejection is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

JOHN F. ENGELHARDT ET AL.

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6959

Date November 28, 2006

By: Janet E. Embretson
Reg. No. 39,665

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 28 day of November 2006.

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